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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments on Proposal to amend the MedWatch Forms to collect post-marketing adverse event data relating to race and ethnicity
68 FR 68402-68403, December 8, 2003
Docket No. 2003N-0529

Dear Sir or Madam:

GlaxoSmithKline (GSK) is a research-based pharmaceutical company engaged in the discovery, development, manufacture, and sale of prescription and over-the-counter pharmaceutical products and vaccines. We appreciate the opportunity to provide comments on the proposal to amend the MedWatch forms to collect post-marketing adverse event data relating to race and ethnicity.

In general, GSK supports FDA's interest in identifying and understanding the roles race and ethnicity play in patients' response to pharmaceutical products and the development of adverse events. We also agree with the concept that capturing race and ethnicity data in structured fields, rather than text fields, would enhance the ability of FDA and applicants to analyze these data. However, we have some concerns relating to the implementation of this initiative as proposed. Our comments and responses to the specific questions raised by FDA in the Federal Register notice are attached.

Thank you for your consideration of these comments.

Sincerely,

Edward N. Pattishall, MD, MPH
Vice President
Global Clinical Safety & Pharmacovigilance

Attachment

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Request for Comments: Amending the MedWatch Forms to collect post-marketing adverse event data relating to race and ethnicity
Docket No. 2003N-0529
December 8, 2003 (FR Vol. 68, No. 235, 68402-68403

On December 8, 2003, the Food and Drug Administration (FDA) published a request for comments on the advantages and disadvantages of systematically collecting race and ethnicity data in post-marketing adverse event reports. FDA also requested comments on whether the MedWatch forms (Forms FDA 3500 and 3500A) should be amended to collect this information using the standardized OMB categories for race and ethnicity. FDA specifically invited comments on the following questions:

1. Should the MedWatch forms be amended with a special field or fields to capture adverse event data on race and ethnicity?
2. Should MedWatch race and ethnicity data distinguish between self-reported and observer-reported designations? If so, how should the designations be captured?
3. Would collection of race and ethnicity data on MedWatch forms have an impact on the ICH E2B guidance relating to the electronic submission of adverse event reports?
4. What is the financial impact associated with adding a special field or fields to the MedWatch forms to collect data on race and ethnicity?

GlaxoSmithKline (GSK) is a research-based pharmaceutical company engaged in the discovery, development, manufacture, and sale of prescription and over-the-counter pharmaceutical products and vaccines. We appreciate the opportunity to provide comments on this proposal.

General Comments and Recommendations

In general, GSK supports FDA's interest in identifying and understanding the roles race and ethnicity play in patients' response to pharmaceutical products and the development of adverse events. We also agree with the concept that capturing race and ethnicity data in structured fields, rather than text fields, would enhance the ability of FDA and applicants to analyze these data. However, we do not believe it is appropriate to amend the MedWatch (FDA 3500 and FDA3500A) forms to collect these data for post-marketing adverse event reports at the present time. We also do not support use of the OMB race and ethnicity categories for collection of this information.

Our major concerns with the proposal include:
- Addition of these fields introduces divergence from international data standards for individual case safety reports
- The OMB categories for race and ethnicity are not applicable internationally
- Due to the voluntary nature of spontaneous post-marketing adverse event reporting, we are concerned about how this information may be used in evaluation of adverse event patterns

Before moving ahead with this initiative, we would urge FDA to consider the following:

- Engage in discussions with relevant international constituencies to develop internationally accepted categories for race and ethnicity. ICH is probably the most effective forum to accomplish this.
- In conjunction with development of internationally agreed race and ethnicity categories, work within ICH to modify the ICH E2B data standards to include race and ethnicity, and to revise the CIOMS I form to include this information. Revision of the MedWatch forms should be accomplished in concert with revision of these other adverse event reporting formats, so that consistent data are provided to regulatory authorities, regardless of the format or origin of the report.

- Finalize the draft guidance for industry, "Collection of Race and Ethnicity Data in Clinical Trials", so that it is also consistent with internationally agreed standards and categories. The same categories for race and ethnicity should be used for both clinical trial and post-marketing reports.
- Due to the sensitive nature of race and ethnicity information, this information should not be mandatory for post-marketing reports, and these fields should be specifically excluded from the "full data set".

Specific Comments

Use of OMB categories for race and ethnicity

Even with structured fields for reporting race and ethnicity data, without standardized categories for race and ethnicity, any analysis would be unlikely to provide scientifically valid data. Although the Federal Register notice refers to the previously issued draft guidance for industry entitled "Collection of Race and Ethnicity Data in Clinical Trials", which recommended use of standardized OMB race and ethnicity categories, no mention is made of the considerable feedback FDA received concerning applicability of these categories internationally. These same comments regarding the international utility of the OMB categories would continue to apply to post-marketing reports. In fact, using the US-focused OMB categories is even more problematic for post-marketing adverse event reporting than for clinical trials, since post-marketing reports emanate from a wide variety of sources in potentially all countries, rather than the limited number of relatively knowledgeable investigators and subjects participating in clinical trials. The OMB categories were developed specifically with US consumers in mind, and despite this fact, it is often difficult to elicit accurate race and ethnicity information from Americans. Using these same categories with non-American consumers and health care providers could reasonably lead to a suggestion that even less accurate data collections may result. Some measure of consistency may be gained by including definitions on the MedWatch form (e.g., Black or African-American (ancestry from sub-Saharan Africa, Afro-Caribbean), Asian (from China, Indochina, Japan, Philippines, Siberia), etc.), but this would add considerable complexity to an already crowded form. The simplified categories outlined in the ICH E5 guidance (Black, white, Asian, other) may be the most appropriate system for this purpose.

We are also concerned that FDA's unilateral adoption of US-focused race and ethnicity categories for post-marketing adverse event reporting, an area that has benefited significantly from international harmonization efforts in the past, may prompt other regulatory authorities to develop their own national criteria for race and ethnicity. Needless to say, this would create an unmanageable situation for multinational pharmaceutical companies such as GSK.

Use of race and ethnicity data in analysis and evaluation of adverse event patterns

As noted above, GSK also has some concerns regarding how race and ethnicity data will be analyzed and used in evaluation of adverse event patterns. Most of these concerns have their basis in the voluntary nature of the spontaneous adverse event reporting system, and include the following:

- The nature of spontaneous adverse event reports is such that, even if appropriate, internationally accepted categories are adopted, attempts to gather race and ethnicity data are unlikely to be consistently successful, thus making it doubtful that the data gathered will be sufficient to conduct scientifically valid analyses. In contrast to clinical trials, where sponsors have the ability to compel investigators to provide requested information, post-marketing adverse event reporting is entirely voluntary on the part of the reporter. Although the spontaneous adverse event system may be effective in identifying signals, these reports do not provide the complete data required for a detailed analysis. There could also be a reporting bias introduced, if people in some racial categories are more willing or able to provide this information than others. This could have adverse consequences with regard to signal detection, as an apparent increase of a particular adverse event in a specific racial group may merely be due to disproportionate reporting from that group.

- The nature and sources of spontaneous reports also raise some questions regarding the reliability and validity of responses to a simple question regarding race/ethnicity, particularly with regard to identifying those of mixed ancestry. Current methodologies for collecting race and ethnicity information in medical genetics studies involve questioning subjects not only about their own race and ethnicity, but also include questions about their first language, and similar information about their biological parents and grandparents. Although we acknowledge that limited information may be better than none, it is highly unlikely that this level of detail can be consistently elicited in the spontaneous reporting environment.
- As with other signals identified by the spontaneous reporting system, any potential signals or patterns of adverse events based on race or ethnicity data would need to be further investigated using epidemiologic or medical genetics studies. We are concerned that we may not be able to confirm or refute such signals via traditional observational pharmacoepidemiologic methods, since race and ethnicity data are not routinely collected or reported in prescription sales data or by the large health insurance databases that are commonly used to further investigate these potential signals.

Our comments on the specific questions raised by FDA follow.

1. **Should the MedWatch forms be amended with a special field or fields to capture adverse event data on race and ethnicity?**

As noted above, we agree that collection of race and ethnicity information in structured fields is preferable to collecting this information in text fields. However, any consideration of additional data fields should reflect the multinational nature of adverse event databases and be based on internationally accepted data standards and categories. Therefore, GSK does not support amending the MedWatch forms to include specific fields for race and ethnicity data as outlined in the proposal. Our reasons for this include:

- Addition of this information is not consistent with internationally agreed data elements for post-marketing adverse event reports. These fields are not included in the internationally recognized CIOMS I form. In addition, the most recently issued ICH guideline, the November 2003 Step 4 ICH guideline on Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting (E2D), does not include race or ethnicity in the list of recommended key data elements for inclusion in expedited reports.
- The change would introduce differences in the data that applicants report to FDA, depending on the reporting format used. Currently, applicants can submit post-marketing adverse event reports to FDA in one of three different formats: the MedWatch (FDA 3500A) form, the internationally accepted CIOMS I form (optional for non-US reports), and electronic submission using ICH E2B format. None of these currently include race and ethnicity fields, and to our knowledge, there are no plans underway to amend either the CIOMS I form or the ICH E2B standards to include these fields.
- GSK currently submits the vast majority of our expedited and periodic post-marketing adverse event reports to FDA electronically, and most of the major pharmaceutical companies are moving in this direction. Given that FDA has consistently advocated for electronic submission in place of paper forms, we find it odd that the Agency is now contemplating revision of a form that is quickly becoming obsolete. In fact, at a recent Drug Information Association meeting, an FDA representative noted that FDA's goal is to have 80% of adverse event reports submitted electronically by the end of 2004. We suggest that the Agency's and industry's resources would be more effectively utilized if they were directed toward enhancing electronic submissions, and/or amending the ICH E2B data fields, rather than revising the Form FDA 3500A.
- Most of the spontaneous reports received by GSK in the US are initially reported by consumers, primarily by telephone. Race and ethnicity are considered sensitive information by many individuals, and probing for this information may actually result in a decrease in our ability to collect information relating to the adverse events experienced by the patient, as consumers may refuse to provide **any** information if they are offended by our questions concerning their race and

ethnicity. If the Agency proceeds with this initiative, applicants will need to do considerable work to determine the best manner to elicit race and ethnicity information without reducing the quantity and quality of information about the adverse event itself.

2. Should MedWatch race and ethnicity data distinguish between self-reported and observer-reported designations? If so, how should the designations be captured?

Should the Agency move ahead with collecting race and ethnicity data for post-marketing adverse event reports, we do not see the need to further classify this information according to the reporter. We do not think that this information would provide any additional value or validation of the racial/ethnic information. We contend that it is scientifically justified to use self-reported racial and ethnic identity information (Burchard EG, et al, The importance of race and ethnic background in biomedical research and clinical practice. NEJM 2003; 348(12):1170-1175 and Rosenberg NA et al, Genetic structure of human populations. Science 2002; 298:2281-2285). The issue of self- versus observer-reported information does raise a question concerning the situation where a patient and their health care provider furnish conflicting race/ethnicity information. If FDA proceeds with these proposals, we request that the Agency provide guidance regarding which reporter takes precedence when contradictory information is provided.

3. Would collection of race and ethnicity data on MedWatch forms have an impact on the ICH E2B guidance relating to the electronic submission of adverse event reports?

As outlined above, there would definitely be an impact on the ICH E2B guidance if FDA were to require submission of race and ethnicity data for post-marketing reports. Since these fields are currently not included in the E2B data standards, there would be a discrepancy in the information provided to FDA when paper forms were used vs electronic submission. There would also be a discrepancy in the information provided to FDA vs that provided to other regulatory authorities, as CIOMS forms and the ICH E2B data standards do not include race/ethnicity information. Since we do see value in collecting and reporting this information in a standard manner, we would urge FDA to work within the ICH framework to develop internationally acceptable categories for race and ethnicity data, and to amend the ICH E2B data standards and guidance accordingly. We do not support FDA proceeding unilaterally to require submission of this information in the US.

4. What is the financial impact associated with adding a special field or fields to the MedWatch forms to collect data on race and ethnicity?

The simple **addition** of these two fields to the MedWatch forms would not incur major financial impact. From GSK's point of view, it would involve redesigning our computer-generated FDA 3500A, and reprogramming the database to output the information in the appropriate place on the redesigned form. Of course, the new form and programming would need to be validated, and the revised computer-generated form would need to be approved by FDA.

However, **implementation** of these two fields would have a much larger financial impact, and would require considerable resource and effort, including the following:

- Although we currently have a field for race in our database, we do not have a separate field for ethnicity. Therefore, a new field and list of values would need to be created, with the associated programming and validation costs.
- Redesign of company data collection forms for spontaneous reports to include this information. Many Operating Companies have developed their own local forms for collecting adverse event information, and many of these are computer-generated. Revising these forms to include fields for race and ethnicity information would also involve reprogramming and validation efforts.

- Assuming that FDA will require use of standard race and ethnicity categories, the lists of values allowable for these fields in our database would need to be revised, and existing values mapped to the new categories and validated. This could have major implications for ongoing clinical trials, as the current categories have been internationally agreed within the company, and are not the same as the OMB categories.
- Considerable effort will need to be expended to train safety personnel worldwide regarding the new fields and categories.
- We are also concerned about the additional resource that will be needed to collect this information, particularly if FDA includes race and ethnicity data in the "full data set". Collecting this additional information and clarifying the ethnicity question with the reporter will add time to every adverse event report we receive by telephone. Including race and ethnicity in the full data set would require applicants to conduct intensive follow-up efforts to obtain the information if it was not initially reported, as described in FDA's proposed rule on Safety Reporting Requirements for Human Drug and Biologic Products (68 FR, March 14, 2003, p 12046).

Conclusions

GSK does support FDA's efforts to identify and understand the roles race and ethnicity play in patients' response to pharmaceutical products and the development of adverse events. We also agree with the concept that capturing race and ethnicity data in structured fields, rather than text fields, would enhance the ability of FDA and applicants to analyze these data. However, GSK does not support addition of structured fields to collect race and ethnicity data to the MedWatch forms (Forms FDA 3500 and FDA 3500A) at the present time. We also do not support use of the OMB race and ethnicity categories for collection of this information. We recommend that FDA work within the ICH framework to develop internationally accepted data standards and categories for collecting race and ethnicity data. Any revisions to the MedWatch forms, particularly the mandatory Form FDA 3500A, should be made in conjunction with similar changes to the CIOMS I form and the ICH E2B data standards.

It might be a useful and educational exercise for FDA to modify the voluntary MedWatch form (FDA 3500) to include fields for race and ethnicity before attempting to modify the mandatory form (FDA 3500A). This could serve as a sort of "pilot program", and provide the Agency with some information regarding completion rates, accuracy, etc. This exercise would not incur any of the costs associated with modifying the FDA 3500A, and would not generate the issues associated with international use of the OMB categories, since voluntary forms are primarily completed manually by US health care providers and patients. However, education of health care providers regarding the correct application of the OMB categories would be needed.